Wivel, Nelson 1996

Dr. Nelson Wivel Oral History 1996

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Dr. Nelson Wivel Interview

Office of NIH History *Oral History Program*

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Bobbi Bennett: Plays back, hopefully it will record too. There. [laughs]

Dr. Nelson Wivel: Okay all right. Well I guess it's a pretty good mic?

BB: Yeah, it is. Now, what is you official title in your new position?

NW: Oh okay, it's Deputy Director of the Institute of Human Gene Therapy at the University of Pennsylvania School of Medicine.

BB: Oh, the School of medicine?

NW: Uh-huh. [affirmative]

BB: And who was – is Wilson –

NW: Jim Wilson is the director.

BB: [coughs] And you start there…?

NW: July 1.

BB: July 1.

NW: Not very long.

BB: Okay.

NW: Oh good, you brought your water. I may go get mine before it's over.

BB: Oh yes. Well, I have asthma.

[break in audio]

BB: A little water happy here. [laughs] And what, essentially, will you be doing?

NW: Well, several things. One, Jim and I are going to co-chair the Research and Development Committee within the institute. That really, basically, manages everything from the bench to clinical trials so we'll really be looking at all phases of the project from the time of its conception until it actually results in a clinical trial, if it does come to that. What happens in the institute is we have a lot of potential projects that may or may not come to fruition. So a frequent way to analyze those is to have somebody give a presentation, an analysis of what he or she proposes to do, and then simply to have a decision tree based on gathering more data or making suggestions on what could be done. So basically, a lot of the projects will begin with the idea of getting to clinical trial but it may be a significant percent [unintelligible]. Obviously one has to look at this process repeated, so we'll spend a fair amount of time doing that.

The other thing that I will have responsibility for is the clinical pathology laboratories. And they do a variety of work to support various research projects. So a lot of the morphometric analysis, the confocal microscopy, the electron microscopy, those sorts of techniques are used to support a lot of the basic science studies. And I'll also have responsibility for overview of the toxicology studies. Clearly, there is a lot of toxicology that has to be done with vectors. Since the major focus of the institute is on that and virus vectors, clearly it is important to determine if new vector gene constructs are freer of [unintelligible] liver pathology than ones have been in the past. So that's a task we'll recur as long as one's developing new vectors.

BB: Is NIH going to set-up vector –

NW: Yeah, there are three labs. Actually, one of those labs is at Penn. The other two, one is at Indiana -- in Cornetta [spelled phonetically] and the other one is in Gary Nabel's [spelled phonetically] shop in Michigan. So those are the three approved vector labs that are funded by NCRR.

BB: So you'll be actually getting [unintelligible]?

NW: We already are. Yeah, those three labs are already, and I -- one of my tasks will be to represent the Institute on the Advisory Committee for NCRR. So I'll be right back [unintelligible]. [laughs]

BB: [laughs] Okay.

NW: As a matter of fact, I think they've got a meeting set up I'm supposed to go to. I can't go, I'm wearing an NIH hat still, but now they've got a meeting the 21st of June where they're going to review six or eight proposed projects. There's an advisory group to NCR which consist of the categorical institutes which are helping to fund these, and then the labs themselves have representatives, and things are presented and reviewed and given priorities and the ones that obviously are most highly ranked would be the ones that will be able to use the service [?]. So there's already a lot of interest in using those to produce vectors for people who are planning to do research in gene therapy.

And let's see, what else? Oh, one of the other things is since I've been fairly active in the international field as a result of this job and have a lot of contacts, I will keep my hand in those organizations with an international nature, which are looking at standards and general principles for research and gene research therapy. Of course, I've had contact with a lot of different countries in Europe and some in Asia, particularly Taiwan and also Japan. So one of my tasks will be to keep abreast of the international scene as far as standards and activities with other countries.

BB: That's good.

NW: Yeah, well actually we never – Jim's had request from other countries with regard to collaborations and so forth. So the institute's well known to other people and across the Atlantic we'd like to be involved [?]. So those things have to be considered.

BB: Sounds like he's getting the ideal person.

NW: Well I – we'll see. We'll see. So yeah [unintelligible]. And I that's about all I think of off the top – there are other things. I'm sure – I told somebody I wash the windows and sweep the cafeteria on Thursday nights, but other than that...

BB: Now, did I hear you tell somebody that this was the only institute for gene therapy?

NW: It's the only institute that's designated as such. There are several gene therapy centers in the country. There's a new one at Mount Sinai School of Medicine, or Dr. Samuel Wu [spelled phonetically] is going to Baylor, to New York to be the director of that. And as I say, there are a number of centers but this is, to my knowledge, is the only the institute that's fully committed to the human gene therapy research. There are probably on the order now of 150 people.

BB: That's a good size.

NW: Yes it's – in fact, it's by far the largest in this country. There's a major commitment on the part of Japan to supporting this research. And you know, deans have to sort of pick and choose. They can't – not everybody can run a supermarket anymore, so certain schools choose to emphasize certain areas. Hence, [unintelligible] obviously made a long-term commitment to support gene transfer studies. So that's why the institute exists.

BB: And you start there July 1st?

NW: Right.

BB: Now, how long have you been at the RAC?

NW: Okay I've been director of this office since August of '89, so just about [unintelligible]. And I was fortunate enough to come in on the very threshold of gene therapy, that was one of the things that was attractive about this job. It seemed to be the very research, which was probably going to come to fruition very shortly and it certainly did. So I've been fortunate enough to see everything from the first protocols through the last that was reviewed.

BB: That's right. [unintelligible].

NW: That's right. So I just happened by circumstance to be there at the beginning and [phone ringing] at the end. Excuse me.

BB: Mmm-hmm.

NW: Yes? Okay. Okay. Bye.

So that -- you know, that was just the circumstance it worked out that way. So it's been an interesting trip to see the beginning of the field and to see it essentially [unintelligible].

BB: Has an announcement been put in the federal register yet?

NW: That's been – it's in Bob Landin's [spelled phonetically] office right now. I think he's finished with it. The federal register notice, which is really the notice of intent, probably should be out by the next week or ten days. It should be on the street maybe within a week. Certainly by ten days I would think.

BB: Did you get much commentary? There were comments from…?

NW: We have had some requests from people who have heard – either heard or read Elliot Marshall's [spelled phonetically] blurb in *Science* and it's not been a large volume. I guess the really critical question is when we open the federal registry notice up for comment then the question will become [unintelligible] how many people will be moved to respond one way or the other. I have no way to predict how that will turn out.

BB: How long are comment periods?

NW: We allow for 15 days. I realize that's not as long as the regulatory agencies do for regulations, but we leave the comment period open for 60 to 90 days, but on the other hand we're not dealing with regulations, we're dealing with a set of guidelines. It's not the same. It's not an entirely analogous situation with regulatory agencies, and since we're not really a regulatory agency we're not really bound by those kinds of rules. So we'll simply see what happens over the course of that period, how many letters we get and what the other opinions are expressed. It's hard to make a conjecture at this point.

BB: Yeah.

NW: Whether there'll be more interest in the press after the federal register notice, I don't know. It's not a document I think that's common everyday reading for most people.

BB: [laughs] No. Now, did you get many press comments after *Science*?

NW: Well we've only had a few and they've been based on the *Science* articles. Perhaps it isn't as widely known. Let's see, that came out yesterday so most everybody will have that issue of *Science* in his hands this week. It remains to be determined how that [unintelligible]. The community itself is obviously well aware of it because the venue where Dr. Varmus was chosen to speak. I think the most active researchers in the field are clearly aware of what's proposed. So request will be for those less involved in the field [unintelligible]. So we'll just have to wait and see.

I don't know -- I would not expect great outpouring response, but my speculations have been in error [laughs] before. I just don't think that it's going to cause that many waves. I think the reason that I feel that is NIH has committed itself to the retention of two important principles and that's why -- a continued venue of public discussion on issues of gene therapy, that's clearly going to be retained, and Dr. Varmus is certainly committed to that. And the second thing is they're going to retain the publicly available database. So I think that for those who have concerns about the RAC being the only model, that it has to be considered that there are other models by which the same end might be achieved. The essence of the importance that public discussion [unintelligible] really what's being relinquished here is review of approval activities which certainly suggest a regulatory tone even though we don't do regulation. There's been a continued argument this now duplicative of [unintelligible]. Relinquishment of that kind of activity then negates that argument.

I think that our feeling -- and I'm thinking now in terms of the director's stance, I think the feeling is that the field has evolved to the extent that it's not necessary for RAC to look at the reviews it did six years ago. At that time, the FDA was just beginning to develop it's own regulatory apparatus for cell and gene therapy. Since that time they have made an obvious commitment, a large commitment of personnel who are devoting their full efforts to regulatory review of cell and gene therapy. So the situation has to be viewed in a dynamic context; that is the regulatory agencies up to speed and running well, and therefore the RAC review of every protocol becomes less critical than it did in the beginning. And I think it's clear that the RAC accomplished several important tasks. They, one, set the scientific and safety standards for the field and the development of the points to consider or the [unintelligible] NIH guidelines. And obviously they have an open review process for gene therapy protocols and they established a public database that allows us to carry out a review of the status of the research in the field.

So those are all important tasks that were carried out very well. I think in my view the RAC has a had a measure of success and it's because of that success that we're now able to consider retiring it from what had been its usual past [?].

There's another element with regard to the new model that I think probably is important to note, that is the gene therapy advisory conferences will have, for the most, part an ad hoc membership. In each case, that membership will be tailored to choosing experts in the particular topic at hand. Now, that gives us a lot more flexibility in terms of discussing something. I like to think of gene therapy as an enabling technology, and as such, because they are really broad spectrum of applications it difficult with a fixed membership such as the RAC has to cover all the areas of application that might come up. So one of the clear-cut attempts to do something that's relevant in the future is to have ad hoc groups of varying backgrounds with a strong scientific focus on a subject that's chosen to be worthy of public discussion. On the other hand, there's a mechanism built into the new system to retain institutional memory and that's the creation of this small board of advisory committee of five to six people who will be actively involved in planning conferences. So in essence there are really two elements in the discussion process: there's the fixed membership [unintelligible] advisory and the ad hoc membership of the individual conferences. So there will be a continuing -- [unintelligible] continuing [unintelligible] advisory committee will be a constant.

BB: And are they likely to be RAC member? Former RAC members?

NW: Well I really don't know just who will be chosen at this point. There's certainly no limitations. At this point we've got [unintelligible] restricted to any group, so it's entirely possible that former RAC members could be included in that process. That certainly would not be inappropriate. But I think, again, it' s a little too early to say just who might be chosen for that.

BB: Because [unintelligible].

NW: I presume so, yeah. Certainly we want him to have a lot of input in and certainly be comfortable with [unintelligible]. So we'll see in the coming weeks how that process works itself out.

BB: Yes, we've already seen post-RAC.

NW: Right, exactly.

BB: Oh, a question, when was the database [unintelligible]? That was during your time, right?

NW: Oh yes, that was done actually about two – two and half years ago we began to do that. Actually the impetus – the driving impetus behind it was the late Bridget Leventhall [spelled phonetically], pediatric oncologist from Johns Hopkins.

BB: I knew her when she was [unintelligible].

NW: Right, so did I. And Bridget felt very strongly that it was of critical importance that in a new field such as this to have some type of monitoring system that would allow us to have periodic looks in the field to determine which experiments were working, which were not working, if there were adverse events. She just felt that it would be perhaps even critical to have this type of information available since gene therapy was in its infancy. Obviously there was agreement on the part of the other RAC members, but I think it's only fair that we recognize her for really this seminal contribution to this concept. In essence she carried the flag on this one.

BB: She was a great lady.

NW: Absolutely, came -- her last RAC meeting was in December and she passed away in the middle of the next January so she really worked right up until the end. An extremely devoted pediatrician.

BB: Yeah, I remember how she used to badger Steve Rosenberg [spelled phonetically].

NW: Right, oh yes. Absolutely.

BB: Submitting his data --

NW: Absolutely. She caused him a few gray hairs.

BB: Deserved a few gray hairs [?].

NW: Absolutely.

BB: Is there anything that you feel like are your major achievements for the RAC?

NW: Oh, I don't think I want to take personal credit for anything that's gone on. I would only credit my staff, credit the hard work and steam [?] they devoted to meeting all the deadlines and all the – taking care of all those not too glamorous by necessary tasks. They made sure all the trains ran on time, but did far more than that. An awful lot of this period has been characterized by the necessity for this office to provide lots of public information, and the staff has been extremely reliable and prompt in providing protocols to investigators and the public, which is no small task, and they did it very well. So I would rather laude them for their efforts than try to claim my own.

BB: Well as far as --

NW: Exactly --

BB: -- cutting down to the Xerox.

NW: That's right. All of the southern half of Canada would be [unintelligible] before we'd accomplished that.

BB: And before RAC, or before GORDA [spelled phonetically] -- who was director when you were there?

NW: There've only been two directors in the history of GORDA which is about just 21 years old, Mr. Bill Gartmen [spelled phonetically], William Gartmen was the first director and he was director for about 13 years and then [unintelligible]. And he was first director of the office when it was actually created by Dr. Fredrickson, and served through a very busy time and when the guidelines were first created in the mid to late '70s they were a fairly stringent series -- they constitute a very stringent series of directors, as became apparent from practice that a lot of the potential problems were not going to materialize, then the guidelines underwent a series of revisions over a period from about '79 to '83 when many of the initial stringencies were removed. This obviously was an era that preceded gene therapy [unintelligible] very active [unintelligible] feels very much in a state of flux [unintelligible] saw all of those changes. It really was only in the early '80s when the question of human genetic engineering, i.e. human gene therapy, was given serious consideration, and two critical events occurred then. One, there was a presidential commission which published a seminal document called "Splicing Life," and following that there were public hearings held by then Congressman Albert H.Gore [spelled phonetically] --

BB: Really?

NW: -- yeah, who had a very public discussion of the potential for human gene therapy and it's ethical implications. And as a result of those hearings the question was asked, "Well is there anybody so constituted who could begin to develop a series of directives for investigators for [unintelligible] wanting to do this type of [unintelligible] research?" It was fairly readily ascertained that the only group in this city that had any relevant experience was the RAC. The RAC accepted this charge and immediately, about 1983, developed a working group, which over the next three years developed a points-to-consider document for [unintelligible]. Actually, Dr. Varmus was an early member of that group and retained his membership on that committee throughout its life. But he actually participated in some of the early discussions, and we were discussing elements of [unintelligible]. That exercise is probably one of the more significant exercises because it represents a case in which a document was developed well in advance of need, because that document was in place before the first proposal for gene transfer research [unintelligible]. So instead of it being a reactive document it was one that was created in advance [unintelligible], which I think is something that doesn't happen too often.

BB: No, it's rare I would say.

NW: It's fairly rare. So that was – that period in the early to mid-'80s was a very important period even though we were obviously [unintelligible].

BB: And when was the first proposal given to the RAC?

NW: Well, actually in 1987 French Anderson and his colleagues presented what we now, in a light tone of voice, call the "phone book." It was actually a very thick document of pre-clinical data that focused on the use of retroviral vectors. That document raised so many questions that it created another couple of years of experiments for these people to do before we felt they could come back to the RAC with a proposal. So actually, the first protocol if you will was – discussions of the first protocol began in 1988. And in October of 1988 the RAC approved what I would call a prologue-type of experiment in that it simply allowed French and Steve Rosenberg to do a preliminary experiment to see if they could safely use retroviral vectors to transfer genes to mammalian cells and to see if they could detect evidence of that transfer and to see if this could be done in a safe way. So that was [unintelligible] in 1988.

The first protocol, the first formal protocol itself was approved July 31st, 1990. And that was quite a whirlwind day because at that time there was the human gene therapy subcommittee as well as the RAC, and the RAC approved that. When it began most of the expertise in gene therapy resided on that subcommittee and there was a more diverse range of expertise on the RAC itself. So a number of the critical reviews were done by people with an interest in gene therapy who were on that subcommittee. But on July 31st the subcommittee met in the morning and the RAC itself met in the afternoon, and the ADA protocol was approved and actually Ashante Desilva [spelled phonetically] was treated at 14 weeks [unintelligible], less than three months after the RAC approval. The first patient was given T-lymphocytes transduced for the wildtype [unintelligible].

BB: Finally, Mike Glaze published the paper.

NW: That's right. That's right, and the paper was appropriately titled, "Review of Four Years of Experience." A few patients treated with [unintelligible] and [unintelligible] much to the relief of all parties concerned. [laughs]

BB: Yes. You think somehow we should phrase in the article that your leaving has nothing to do with desertion of RAC?

NW: Yeah I would say upfront because without getting into all the specifics I began a discussion to do this far, far in advance of anything in the way of any decision making in regard to the future if the RAC, and I'm leaving because there are excellent professional opportunities related to my background and experience. That's the sole driving force of [unintelligible]. I wasn't necessarily looking to leave at that time. Certainly, although I had 30 years of the commission before it was planned that I would transfer to civil service. Things were designed so that I could continue here if I desired, that was by design. So I'm leaving strictly because it's a good professional opportunity. Like I say, I – off the record, I began those discussion after Thanksgiving last year. So that was even before the December RAC meetings. And I could not – no way -- I could not predict at that point anybody was going to be [unintelligible]. So I think the two events have to be properly viewed as disparate [unintelligible] relationship. I'm sure the press will ask you that.

BB: Oh yes, yes.

NW: Elliot Marshall [spelled phonetically] has already gone ahead and made his own interpretation, which annoyed me a little bit.

BB: Yeah, reporters feel they have the right to do this.

NW: Well he has a qualifier he said he "voted against in a way" and I'm sure if he were pressed on that he would say, "I didn't say it was a direct relationship. It was indirectly relevant." [unintelligible]

BB: Yes.

NW: So I don't think it's worth responding to his interpretation because we did not – we have never discussed that at all. [unintelligible]

BB: Yes.

NW: There will always be those people who will say that. So be it.

BB: So be it, right, right. So you're actually retiring from the commission?

NW: Yeah.

BB: I mean, that would be the correct way to put it?

NW: Yeah, or I -- yeah I would just I'm leaving to pursue a second career. [laughs]

BB: [laughs] Okay.

NW: Because lots of people –

BB: After 30 years.

NW: -- yeah, lots of people retire from the Corps and go on to – it's a fairly common track at NIH.

BB: Yeah. Well I thought – wasn't there sort of a mandatory –

NW: Well they – well they're trying to get more and more people to leave and as you may have noticed Steve Rosenberg has left the Corps, Toni Fauci is not leaving is director of NIAID now, he's withstanding those yellow sheets. He's simply transferring from the Corps to take an SES position. And there are numerous others who've done that -- [unintelligible], Mike Potter [spelled phonetically]; there's quite a large number of people that have transferred to the [unintelligible] service. The reason why – I was given a choice. I was given a choice to either stay in the Corps or transfer, and I elected to transfer because you have to apply every year and go through the same routine in order to justify yourself, and that is more paperwork and bureaucracy than it's worth for NIH to go through that. So if you want to say that's part of their design to encourage people to leave after 30 years, I guess that might be a relevant observation, but in effect that's what's happening, the vast majority of people who stay at NIH now after 30 years are transferred [unintelligible]. And I think there's clearly an intent on the part of the Corps to encourage this because at one point practically everybody at NIH who stayed on – some of them as much as 5, 6, 7, 8, 10 years after 30 [unintelligible] would like to see that kind of thing. But off the top of my head I mentioned a half a dozen, certainly Steve Rosenberg [unintelligible] about the same seniority [unintelligible]. So yeah, I would characterize it as a move to another career. [laughs]

BB: Right, okay. And it doesn't sound like you're going to have any free time.

NW: No, no I – I work lots of 12-hour days, I don't think there's going to be much question, everybody works very hard at that institute. 12-hour days are the norm. There's a tremendous investment in that as a research entity, and people [unintelligible]. So there's a real commitment of the people up there to [unintelligible]. I don't look for things to be any quieter than they have been in this office, and this office doesn't get very quiet either. So hopefully it was good training.

BB: [laughs] Yes. Often in these retirement stories they put in quotes from either a boss or a coworker, people who [unintelligible] and I was wondering should we get – ask French or Mike [unintelligible]?

NW: That's all right with me. I have no problem. Just remember that French is not wanting to give up the RAC so –

BB: Oh.

NW: -- his will be – well that's all right. I mean it's couched – it'll be couched from that context I'm sure, and that's okay but I'm just thinking of Elliot's article and French's thing saying it was "premature, inappropriate," and he had this one other element in the series. But that's certainly – Mike Glaze, maybe, has made less public commitment to the future of the RAC.

BB: Well maybe we'll ask him.

NW: Yeah, and he's close by and you may be able to get him more easily than French who tends to fly around quite a bit. [unintelligible] away from his home base. But I -- you know, [unintelligible].

BB: Sort of as the [unintelligible] gene therapy researchers.

NW: Right, right.

BB: I think we will [unintelligible].

NW: Yeah, I think unfortunately French might take this another platform, and I -- you know – well, you never know what French is going to say. He might say inopportune things about the future of the office.

BB: Oh, we wouldn't have to put it in.

NW: Yeah, but you –

BB: Yeah, we might get into it.

NW: Yeah, you might get into soapbox here, so [unintelligible]. Because he obviously feels -- he and Abby Myers [spelled phonetically] visited several congressmen and senators on Capitol Hill and lobbied on behalf of the RAC about three weeks ago before any announcement had been made. So they are clearly committed to the preservation of that entity.

BB: Yeah I figured Abby [unintelligible].

NW: Very much so. She doesn't think that you can trust anyone. So that's –

BB: No.

NW: And I think that…

[end of transcript]